Gold-Catalyzed Oxidative Coupling of Arenes and Arylsilanes

Organic Syntheses

Gold-Catalyzed Oxidative Coupling of Arenes and Arylsilanes

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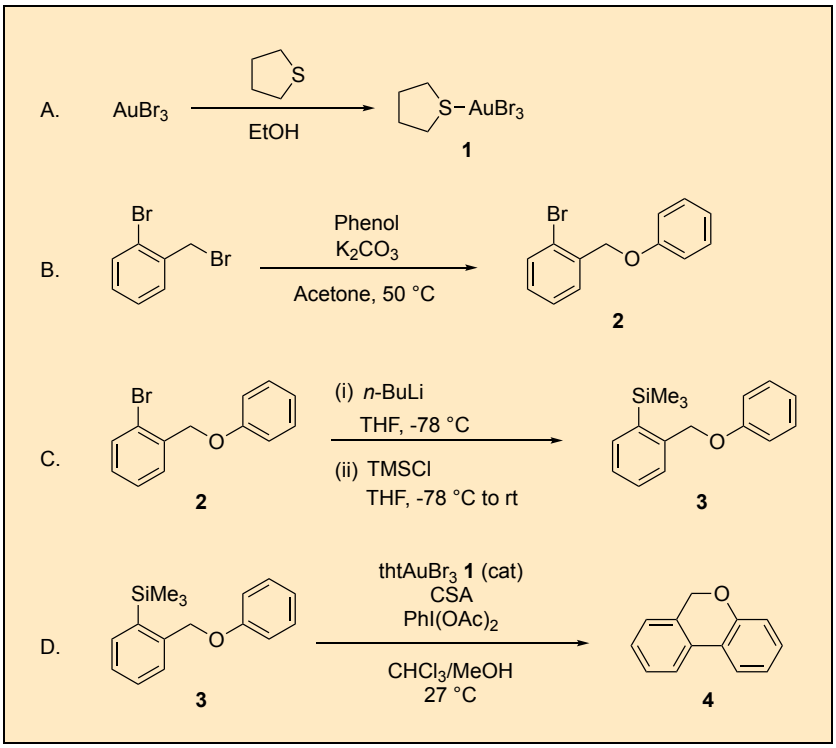

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Procedure (Note 1)

A. *Tetrahydrothiophene gold(III) bromide (thtAuBr$_3$) (**1**).* A 100 mL, single-necked round-bottomed-flask (RBF) equipped with a Teflon-coated magnetic stir bar (12 x 25 mm, oval) is charged with $AuBr_3$ (1.0 g, 2.3 mmol, 1.0 equiv) (Notes 2 and 3) followed by EtOH (20 mL) (Note 4) and the mixture is stirred (400 rpm, under air) for 1 min at 23–25 °C. Tetrahydrothiophene (222 mg, 222 μL, 2.5 mmol, 1.10 equiv) (Note 5) is dissolved in EtOH (3 mL) in a 5 mL vial and added dropwise to the $AuBr_3$ solution over ~3 min, forming a red crystalline precipitate (Figure 1A). The vial is rinsed with additional EtOH (1 mL) and this is added to the reaction mixture in one portion. After stirring for an additional 3 min, heptane (70 mL) (Note 6) is added in one portion. The RBF is then placed in an acetone bath cooled with liquid nitrogen (roughly –80 °C) (Note 7) and stirred for 3 min (400 rpm) (Figure 1B). The resulting precipitate is collected by vacuum filtration (55 mm filter paper) (Note 8) to give a dark red-brown solid (Figure 1C). The RBF is rinsed with heptane (~20 mL) using a wash bottle, and the remaining material is also collected by filtration. The combined solids are then washed with heptane (3 × 20 mL) and transferred to a 100 mL RBF by dissolution through the filter paper with CH_2Cl_2 (~70–80 mL, in portions) (Note 9) before concentration by rotary evaporation at 40 °C (550 to 7.5 mmHg) to give a red-brown solid (1.14 g, 95 % mass return). Hot (90 °C) toluene (52 mL, 45 mL/g) (Note 10) is added to the 100 mL RBF, and this solution is swirled by hand to dissolve material on the sides of the flask. Once the majority of material is dissolved, the RBF is placed in an oil bath at 90 °C while a filtration apparatus is prepared. A hot filtration is carried out collecting the filtrate in a conical flask (Note 11), the RBF is rinsed with additional hot toluene (~3 mL, 3 mL/g) and this is also filtered. The conical flask is placed in the oil bath at 90 °C and the solution is stirred (Teflon-coated cylindrical magnetic stirbar, 8 x 30 mm, 400 rpm) for 2 min, hot (~90 °C) heptane (17 mL, 15 mL/g) is added over ~1-2 min with stirring. The conical flask is removed from the oil bath and the dark red solution is allowed to cool at 23–26 °C over 1 h. The opening of the flask is covered with Parafilm M before being placed in a fridge (0 °C) for 3 h then moved to a freezer (–20 °C) overnight (~16 h). The resulting crystals are collected by filtration using a Hirsch funnel (filter paper 1 cm diameter, house vacuum) (Figure 1D). Crystals remaining in the conical flask are rinsed onto the filter paper using a wash bottle filled with heptane:toluene 4:1 (~20 mL) and the combined crystals are washed with additional heptane:toluene 4:1

(2 x 15 mL). The crystals are then dried on the Hirsch funnel under vacuum with an inverted funnel dispensing nitrogen gas for 5 min. The resulting dark-red needles are collected in a vial and stored in the fridge (0.97 g, 80%) (Figure 1E) (Notes 12 and 14).

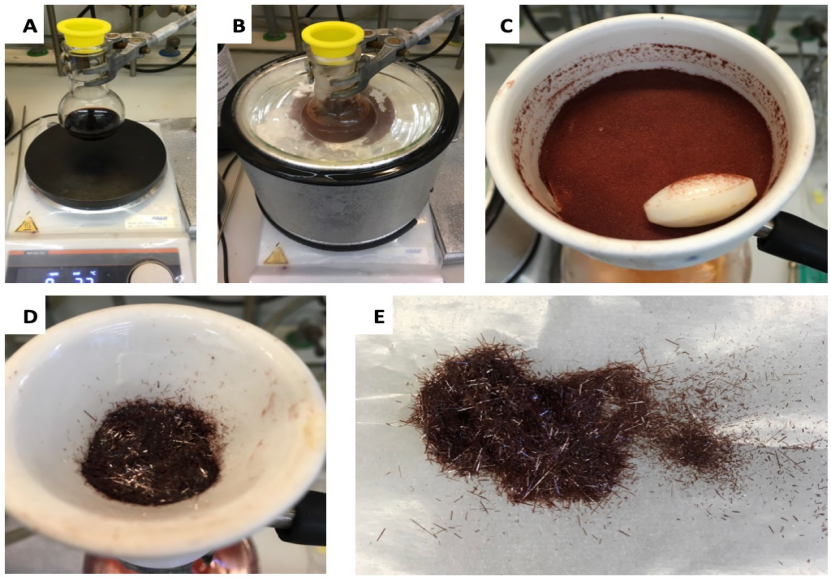

Figure 1. (A) Reaction mixture after addition of tetrahydrothiophene. (B) Reaction mixture after addition of heptane in liquid nitrogen/CO_2 bath. (C) Crude material collected by filtration. (D) Recrystallized material collected on a Hirsch funnel. (E) Crystalline material as medium-large dark red needles.

B. *1-Bromo-2-(phenoxymethyl)benzene* (**2**). A 500 mL, single-necked round-bottomed flask (RBF) equipped with a Teflon-coated magnetic stir bar (15 x 35 mm, oval) is charged sequentially with acetone (200 mL) (Note 14), K_2CO_3 (11.1 g, 80.3 mmol, 1.6 equiv) (Note 15), phenol (7.06 g, 75 mmol, 1.5 equiv) (Note 16) and 2-bromobenzyl bromide (12.5 g, 50 mmol, 1 equiv) (Note 17). The RBF is fitted with a reflux condenser (air cooling only) and placed in an oil bath heated to 50 °C (Figures 2A and B). The reaction mixture is stirred (500 rpm) at this temperature over 18 h (Figure 2C). The RBF is removed from the oil bath and allowed to cool to 23–25 ºC with stirring (~30 min). The reaction mixture is filtered through a sintered glass funnel (pore size 3) under suction (vacuum) and the RBF/K_2CO_3 is rinsed with

acetone (2 x 30 mL) which is also filtered. The combined filtrates are concentrated by rotary evaporation at 40 °C (300 to 75 mmHg) and dried under high vacuum pump (<1 mmHg) to remove any trace of acetone. The crude material is dissolved in petroleum ether (bp 40–60 °C, 20 mL) (Note 18) and passed through a silica gel plug (Figure 2D) (Notes 19 and 20) under vacuum. The RBF containing the crude material is rinsed with additional petroleum ether (bp 40–60 °C, 2 x 20 mL) and this is also passed through the silica gel plug. Remaining product is eluted through the plug with petroleum ether (bp 40-60 °C, 350 mL) under suction and the filtrate is concentrated by rotary evaporation at 40 °C (300 to 7.5 mmHg) to obtain 13.02 g (99%) of 1-bromo-2-(phenoxymethyl)benzene (**2**) as a clear, colorless oil which can spontaneously solidify over time to provide a white crystalline solid (Figures 2E and 2F) (Notes 21 and 21).

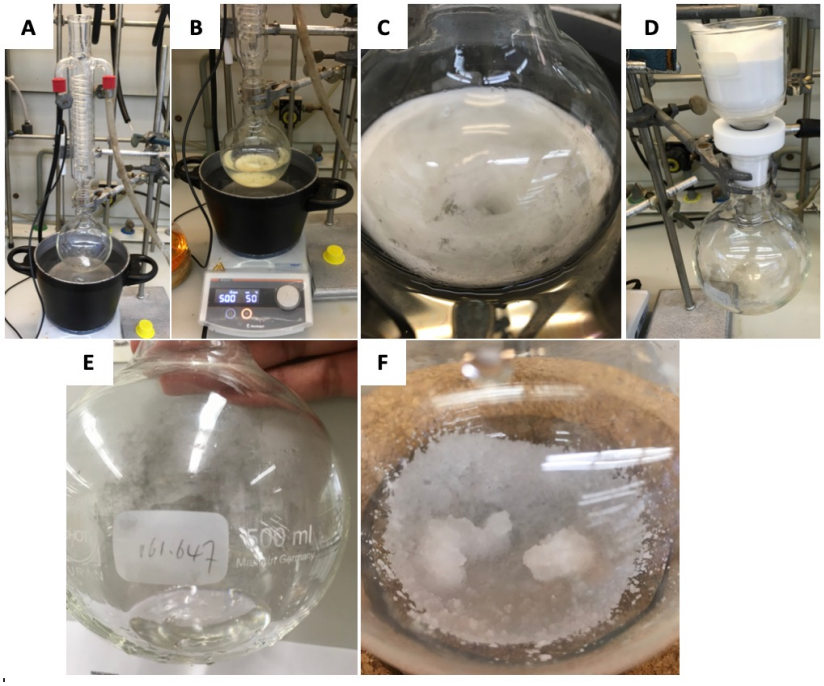

Figure 2. (A) Reaction mixture before addition of all reagents. (B) Reaction mixture after addition of all reagents. (C) Silica gel plug topped with pad of cotton wool. (D) Pure material as an oil. (E and F) Pure material as a crystalline solid.

C. *1-Trimethylsilyl-2-(phenoxymethyl)benzene (**3**)*. A dry, 250 mL, two-necked RBF equipped with a Teflon coated magnetic stir bar (15 x 35 mm, oval), a nitrogen inlet and a rubber septum is placed under a nitrogen atmosphere and maintained this way over the course of the reaction. 1-Bromo-2-(phenoxymethyl)benzene (**2**) (13.0 g, 49.4 mmol, 1 equiv) from the previous step is dissolved in THF (30 mL) (Note 23) and transferred to the 2-necked RBF via a syringe fitted with a wide bore needle (gauge 14). Remaining **2** is dissolved in additional THF (2 x 20 mL) and added to the 2-necked RBF in the same manner (Figures 3A and B). Additional THF (30 mL) is added and the RBF is placed in a dry ice/acetone bath at –78 °C and stirred (350 rpm) (Figure 3C). *n*-BuLi (2.25 M in hexanes, 22.9 mL, 51.5 mmol, 1.04 equiv) (Note 24) is added slowly via syringe over ~15 min (Note 25), causing the reaction mixture to develop a pale orange/yellow color (Figure 3D). The reaction is stirred for 5 min at –78 °C before addition of TMSCl (7.6 mL, 60 mmol, 1.2 equiv) (Note 26) over ~5 min (Note 27) via syringe, resulting in a colorless solution (Figure 3E). The RBF is removed from the dry ice/acetone bath and allowed to warm to 23–26 °C with stirring over ~45 min (Figure 3F). The reaction mixture is quenched with deionised water (20 mL), transferred to a 250 mL separating funnel using Et_2O (~30 mL) (Note 28) to rinse the RBF and the layers are separated.

The aqueous layer is extracted with Et_2O (30 mL) and the combined organic portions are washed with brine (30 mL) (Note 29), dried over magnesium sulfate (5 g) for 5 min (Note 30) and then filtered through a funnel plugged with cotton wool. The flask is rinsed with Et_2O (30 mL) and this is also passed through the cotton wool plug before concentration by rotary evaporation at 40 °C (600 to 7.5 mmHg). The crude product is filtered through a silica gel column (5 x 30 cm, 100 g of silica gel, ~5 cm high) using petroleum ether (bp 40–60 °C):toluene (4:1). The crude material is loaded onto the column in petroleum ether (bp 40–60 °C, 15 mL) and the sides of the column are rinsed with additional petroleum ether (bp 40–-60 °C, 10 mL). The first 500 mL are collected in RBF and concentrated by rotary evaporation at 40 °C (600 to 7.5 mmHg) to give 1-trimethylsilyl-2-(phenoxymethyl)benzene (**3**) as a clear, colorless oil (12.1 g, 96%) (Figures 3G, 3H, and 3I) (Notes 31, 32 and 32).

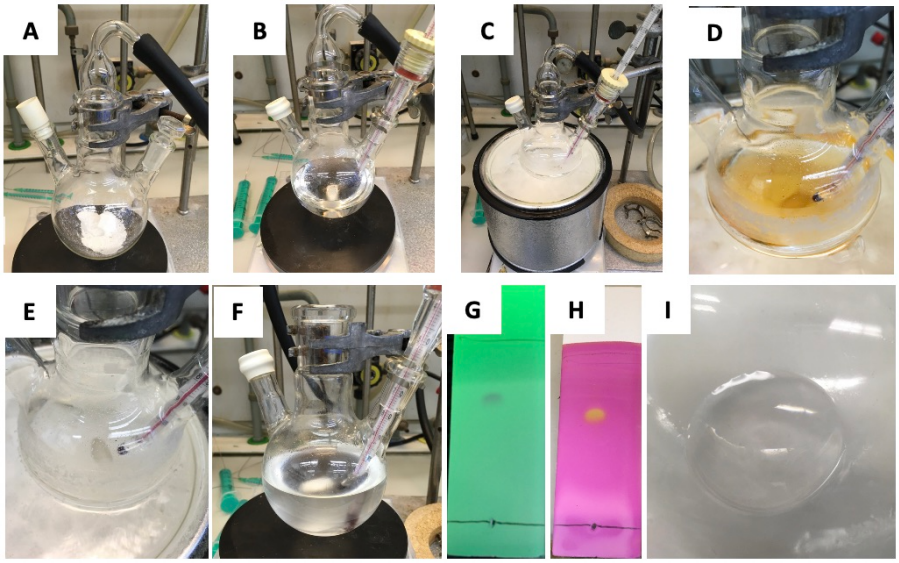

Figure 3. (A) Set up of the reaction with 1-bromo-2-(phenoxymethyl)benzene. (B) Solution of 1-bromo-2-(phenoxymethyl)benzene in THF. (C) Reaction mixture in a bath at -78 °C. (D) Reaction mixture after addition of *n*-BuLi. (E) Reaction mixture after addition of TMSCl. (F) Warming to room temperature. (G) TLC by fluorescence quenching at 254 nm (from checkers). (H) TLC after staining with $KMnO_4$ solution (from checkers). (I) Pure material as an oil.

D. *6H-Benzo[c]chromene (**4**).* A 1 L, single-necked RBF equipped with a Teflon-coated magnetic stirbar (15 x 35 mm, oval) is charged with 1-trimethylsilyl-2-(phenoxymethyl)benzene (**3**) (8.5 g, 33.1 mmol, 1 equiv), $CHCl_3$ (660 mL) (Note 33) and MeOH (6.6 mL) (Note 35). The RBF is placed in an oil bath at 27 °C and stirring is begun (450 rpm). Compound **1** (thtAuBr_3) (174 mg, 0.33 mmol, 1 mol%) is added and allowed to dissolve over ~3 min (Figure 4A), which is followed by the addition of (±)-camphor-10-sulfonic acid (10.0 g, 43.0 mmol, 1.3 equiv) (Note 36) and (diacetoxyiodo)benzene (11.7 g, 36.3 mmol, 1.1 equiv) (Note 37) (Figure 4B). The reaction mixture is then sealed with a rubber septum and pierced with a short needle. If desired, the reaction can be monitored by TLC (Notes 38 and 39). After ~2 h the reaction mixture precipitates black particles, indicating consumption of the oxidant and the reaction endpoint (Figure 4C). The reaction mixture is

transferred to a 1 L separating funnel and partitioned with sat. aq. Na_2CO_3 (150 mL) (Note 40). The layers are separated and the organic layer is washed with brine (150 mL), dried over magnesium sulfate (3 g) for 5 min and then filtered through a funnel plugged with cotton wool (Note 41). The flask is rinsed with $CHCl_3$ (20 mL) and this is also passed through the cotton wool before concentration by rotary evaporation at 40 °C (300 to 7.5 mmHg). This

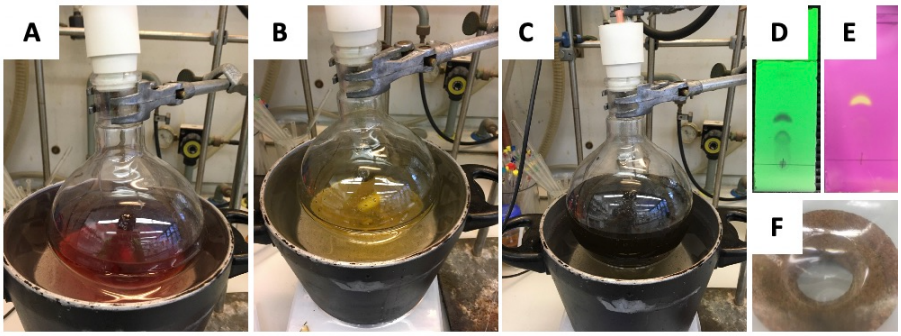

Figure 4. (A) Reaction mixture after addition of thtAuBr$_3$. (B) Reaction mixture ~15 min after addition of IBDA and CSA. (C) Reaction mixture after ~2 h, with black precipitate indicating the endpoint. (D) TLC at the endpoint by fluorescence quenching at 254 nm. (E) TLC at the endpoint after staining with KMnO$_4$ solution. (F) Pure material as an oil.

material is purified by flash chromatography on a silica gel column (8 x 30 cm, 500 g of silica gel, ~25 cm high). The column is equilibrated using petroleum ether (bp 40–60 °C):Et_2O (97:3), the crude material loaded onto the column in petroleum ether (bp 40–60 °C) (5 mL) and eluted with 1.0 L of petroleum ether (bp 40–60 °C):Et_2O (97:3) followed by 1.0 L of petroleum ether (bp 40–60 °C):Et_2O (96:4) and 500 mL of petroleum ether (bp 40–60 °C):Et_2O (95:5). The first ~1.5 L is discarded, then fractions are collected in test tubes (25 mL volume). The desired product is obtained in fractions 20-51 (Notes 42 and 43). These are concentrated by rotary evaporation at 40 °C (375 to 7.5 mmHg) to give *6H*-benzo[c]chromene as a clear oil (4.07 g, 68%) (Figure 4F (Notes 44 and 44).

Notes

1. Prior to performing each reaction, a thorough hazard analysis and risk assessment should be carried out with regard to each chemical substance and experimental operation on the scale planned and in the context of the laboratory where the procedures will be carried out. Guidelines for carrying out risk assessments and for analyzing the hazards associated with chemicals can be found in references such as Chapter 4 of "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at https://www.nap.edu/catalog/12654/prudent-practices-in-the-laboratory-handling-and-management-of-chemical). See also "Identifying and Evaluating Hazards in Research Laboratories" (American Chemical Society, 2015) which is available via the associated website "Hazard Assessment in Research Laboratories" at https://www.acs.org/content/acs/en/about/governance/committees/chemicalsafety/hazard-assessment.html. In the case of this procedure, the risk assessment should include (but not necessarily be limited to) an evaluation of the potential hazards associated with gold tribromide, ethanol, tetrahydrothiophene, heptane, acetone, dichloromethane, toluene, dimethylsulfone, potassium carbonate, phenol, 2-bromobenzyl bromide, petroleum ether, silica gel, tetrahydrofuran, n-butyllithium, diphenylacetic acid, chlorotrimethylsilane, diethyl ether, sodium chloride, magnesium sulfate, potassium permanganate, chloroform, methanol, camphor-10-sulfonic acid, (diacetoxyiodo)benzene and sodium carbonate. Step B involves the use of phenol which is highly toxic. Step C involves the use of n-butyllithium, this is pyrophoric and must be handled with care.
2. Gold tribromide (99%) was purchased from Alfa-Aesar and used as received.
3. Gold tribromide is hygroscopic and we have found the reagent quality to vary greatly with age, even when stored in sealed vials. If poor yields are obtained when using an older bottle, we recommend dissolving the crude material in acetonitrile, filtering off any insoluble precipitate and then concentrating the filtrate by rotary evaporation. Older material purified in such a way and used following the procedure outlined in this manuscript generally provided ~70% yield of thtAuBr$_3$.

4. Ethanol, absolute analytical reagent grade (>99%) was purchased from Fisher Scientific and used as received.
5. Tetrahydrothiophene (99%) was purchased from Sigma-Aldrich and used as received.
6. Heptane (99%) was purchased from VWR chemicals and used as received.
7. A dry ice/acetone bath can be used instead, but insertion of the 100 mL RBF causes intense bubbling which can result in small quantities of acetone entering the RBF.
8. MACHEREY-NAGEL filter paper was used.
9. Dichloromethane, analytical reagent grade (>99%) was purchased from Fisher Scientific and used as received.
10. Toluene, ACS reagent grade (≥99.7%) was purchased from Sigma-Aldrich and used as received.
11. The submitters used a preheated 250 mL conical flask and 60 mm diameter glass funnel, obtained from an oven set at 100 °C for ~15 min. A small piece of cotton wool soaked in hot toluene was used to plug the funnel.
12. A reaction performed on half-scale provided 0.5 g (83%) of the dark red needles. Tetrahydrothiophene gold(III) bromide (thtAuBr$_3$) characterization data: mp = 142–145 °C (toluene:hexane, 3:1); ^{1}H NMR (400 MHz, CD_2Cl_2) δ : 2.13 – 2.26 (m, 2H), 2.29 – 2.42 (m, 2H), 3.30 – 3.36 (m, 2H), 4.11 – 4.18 (m, 2H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ : 30.5, 43.7; IR (neat) 3006, 2935, 2858, 2354, 1738, 1437, 1416, 1255, 1136, 954, 877, 799 cm^{-1}; HRMS EI-MS *m*/*z* calcd for $C_4H_8AuBr_3S$: 521.75569 [M]+; found 521.75477.
13. The weight percent (wt%) purity was determined to be 98.6 wt% by quantitative ^{1}H NMR (QNMR) using dimethylsulfone purchased from Sigma-Aldrich as an internal standard (99.96 wt%).
14. Acetone, ACS reagent grade (≥99.8%) was purchased from VWR and used as received.
15. Potassium carbonate, anhydrous, (99%) was purchased from Fisher Scientific and used as received.
16. Phenol, unstabilized, ReagentPlus (≥99%) was purchased from Sigma-Aldrich and used as received.
17. 2-Bromobenzyl bromide (99%) was purchased from Fluorochem and used as received.

18. Petroleum ether (BP 40-60, >99%) was purchased from Fisher Scientific and used as received.
19. Silica gel (40-63 μm) was purchased from Merck and used as received.
20. The submitters used a sintered glass funnel measuring 5 cm high x 5.5 cm diameter packed with silica gel up to ~3 cm high and topped with a small pad of cotton wool to protect the silica surface (Figure 2B).
21. A reaction performed on half-scale provided 6.47 g (98%) of a colorless oil. 1-Bromo-2-(phenoxymethyl)benzene (**2**) characterization data mp = 46–48 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.15 (s, 2H), 6.97 – 7.02 (m, 3H), 7.19 (td, *J* = 7.9 and 1.7 Hz, 1H), 7.30 – 7.36 (m, 3H), 7.56 – 7.61 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ : 69.3, 114.9, 121.2, 122.2, 127.6, 128.9, 129.2, 129.5, 132.6, 136.4, 158.4; IR (neat) 3055, 1738, 1591, 1493, 1444, 1373, 1240, 1023, 743, 688 cm^{-1}; HRMS EI-MS *m*/*z* calcd for $C_{13}H_{11}ONaBr$: 284.98855 [M]+; found 284.98811.
22. The weight percent (wt%) purity was determined to be 98.7 wt% by quantitative ^{1}H NMR (QNMR) using dimethylsulfone purchased from Sigma-Aldrich as an internal standard (99.96 wt%).
23. Tetrahydrofuran (>99.8%, unstabilized) was purchased from Sigma Aldrich and dried by passage through an activated alumina column under argon in a solvent purification system.
24. *n*-Butyllithium (2.5 M in hexanes) was purchased from Acros Organics and titrated before use with diphenylacetic acid (2 mmol) in tetrahydrofuran (15 mL) at room temp (approx. 20 °C in a water bath) until the appearance of a consistent yellow color.[2] This was performed in duplicate.
25. The internal temperature was kept below –65 °C.
26. Chlorotrimethylsilane (98%) was purchased from Sigma-Aldrich and purified by distillation over calcium hydride under N_2 before use.
27. The internal temperature kept below –60°C.
28. Diethyl ether (>99%) was purchased from Fisher Scientific and used as received.
29. Sodium chloride (99%) was purchased from Fisher Scientific and used as received.
30. Magnesium sulfate (anhydrous, 99%) was purchased from Fisher Scientific and used as received.
31. The fractions should be checked by TLC analysis (TLC Silica gel 60 F_{254}, aluminum backed sheets purchased from Merck) with petroleum ether (bp 40-60):toluene (4:1) as eluent. Staining with $KMnO_4$ (1.5 g $KMnO_4$,

10 g K_2CO_3 and 1.25 mL 10% wt/v NaOH in 200 mL water) allows visualization of minor impurities.

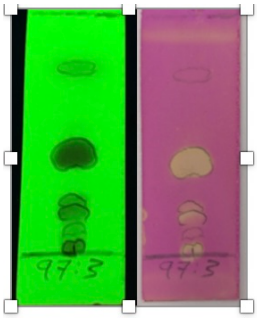

Figure 5. TLCs obtained by submitters.

Product R_f = 0.50, impurities at ~0.60 and ~0.40. The submitters found the impurities were often not visible by TLC analysis of the crude material due to the low relative concentrations, however, they were visible in the early and final product-containing fractions obtained during column chromatography (see Figure 5).

32. A second reaction on half-scale provided 6.5 g (98%). 1-Trimethylsilyl-2-(phenoxymethyl)benzene characterization data: ^{1}H NMR (400 MHz, $CDCl_3$) δ : 0.36 (s, 9H), 5.11 (s, 2H), 6.98 – 7.01 (m, 3H), 7.31 – 7.37 (m, 3H), 7.42 (td, *J* = 7.5, 1.5 Hz, 1H), 7.51 (dd, *J* = 7.5, 0.5 Hz, 1H), 7.62 (dd, *J* = 7.3, 1.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 0.3 (3C), 70.3, 114.7 (2C), 120.9, 127.4, 128.7, 129.4, 129.5 (2C), 134.8, 138.8, 142.0, 158.7; IR (neat) 2956, 1738, 1598, 1493, 1373, 1233, 1128, 1079, 1031, 834, 750, 688, 617 cm^{-1}; HRMS EI-MS *m*/*z* calcd for $C_{16}H_{20}ONaSi$: $[M]^+$; 279.11756, found; 279.11805.
33. The weight percent (wt%) purity was determined to be 98 wt% by quantitative ^{1}H NMR (QNMR) using dimethylsulfone purchased from Sigma-Aldrich as an internal standard (99.96 wt%).
34. Chloroform, analytical reagent grade (>99%), containing amylene as stabilizer, was purchased from Fisher Scientific and passed through a short (6 cm tall x 4 cm wide) column of activated, basic alumina, Brockmann grade 1 before use.
35. Methanol, anhydrous (99.8%) was purchased from Sigma-Aldrich and used as received.

36. (±)-Camphor-10-sulfonic acid (98%) was purchased from Alfa-Aesar and used as received.
37. (Diacetoxyiodo)benzene (98%) was purchased from Sigma-Aldrich and used as received.
38. The gold-catalyzed coupling may be run open to the air without a rubber septum. The purpose of a rubber septum pierced with a needle in this case is simply to prevent extraneous matter from entering the reaction flask.
39. The reaction progress may be checked by TLC analysis (TLC Silica gel 60 F254, aluminum backed sheets purchased from Merck) with petroleum ether (bp 40-60 °C):Et_2O (97:3) as eluent. Staining with $KMnO_4$ (1.5 g $KMnO_4$, 10 g K_2CO_3 and 1.25 mL 10% wt/v NaOH in 200 mL water). Product R_f = 0.37, starting material R_f = 0.55 (Figure 4D and E).
40. Sodium carbonate (anhydrous, >99%) was purchased from Fisher Scientific and used as received.
41. The separatory funnel needs to be cleaned in-between washes to remove any black residue.
42. The fractions should be checked by TLC analysis (TLC Silica gel 60 F_{254}, aluminum backed sheets purchased from Merck) with petroleum ether (bp 40-60 °C):Et_2O (97:3) as eluent. Staining with $KMnO_4$ (1.5 g $KMnO_4$, 10 g K_2CO_3 and 1.25 mL 10% wt/v NaOH in 200 mL water). Product R_f = 0.37 with closely eluting impurities above and below. The submitters found the impurities were often not visible by TLC analysis of the crude material due to the low relative concentrations, however, they were visible in the early and final fractions of product during column chromatography.
43. Obtaining material of ≥97% purity is quite challenging at this scale due to closely eluting impurities both above and below the target compound. Thus, fractions should be combined only after inspection by TLC. The submitters found on 1/4 the reported scale, with 200 g of silica gel, the product was obtained in 89% yield with 97% purity. For more polar substrates, separation improves dramatically and allows facile purification by chromatography.
44. A reaction performed on half scale provided 2.15 g (71%) of the product as a clear oil. *6H*-Benzo[c]chromene characterization data: ^{1}H NMR (400 MHz, $CDCl_3$) δ : 5.14 (s, 2H), 7.01 (d, *J* = 8.1 Hz, 1H), 7.07 (td, *J* = 7.5, 0.9 Hz, 1H), 7.16 (d, *J* = 7.4 Hz, 1H), 7.23 – 7.31 (m, 2H), 7.39 (t, *J* = 7.6 Hz,

1H), 7.71 (d, *J* = 7.8 H, 1H), 7.75 (d, *J* = 7.7, 1.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 68.4, 117.4, 122.0, 122.1, 122.9, 123.3, 124.6, 127.6, 128.4, 129.4, 130.1, 131.4, 154.8; IR (neat) 2971, 2851, 1738, 1605, 1486, 1437, 1366, 1240, 1199, 1016, 757, 750, 722 cm^{-1}; LRMS EI-MS *m*/*z* calcd for $C_{13}H_{10}O$: $[M]^+$; 182.07262, found; 182.07162.

45. The weight percent (wt%) purity was determined to be 97 wt% by quantitative ^{1}H NMR (QNMR) using dimethylsulfone purchased from Sigma-Aldrich as an internal standard (99.96 wt%).

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

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Discussion

*Inter*molecular Coupling of Arenes and Aryl Silanes

Overview

The biaryl motif is widely recognized as an important feature in many key areas of chemistry, from pharmaceuticals to materials chemistry and agrochemicals. As a result of this important bond, and the petrochemical nature of most feedstock, the retrosynthetic disconnection of the biaryl link is both intuitive and economical. In line with this, we have recently reported a gold-catalyzed direct arylation of moderately electron-rich arenes (Ar^1-H) with aryl silanes (Ar^2-$SiMe_3$) (Scheme 1).[3] High regio- and chemoselectivity based on S_EAr reactivity is observed, with the important consequence that the site of arylation is predictable from well-understood electronics considerations. Complementary reactivity is observed compared to alternative direct arylations that proceed via deprotonation and favor electron-poor substrates. Furthermore, mild conditions are employed, typically 1-2 mol% of an environmentally benign Au catalyst, under air, at room temperature, with reagent grade solvents and a commercially available terminal oxidant.

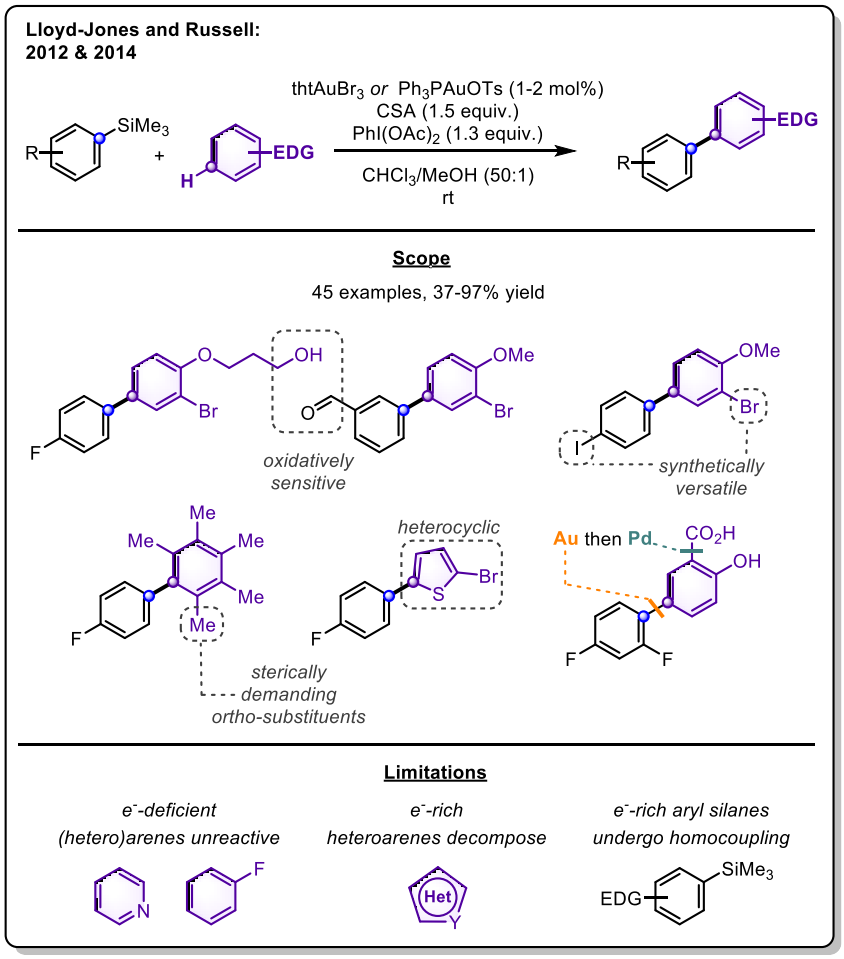
Scope

The reaction partners (Ar^1-H and Ar^2-$SiMe_3$) may possess a diverse range of functionality including; esters, ethers, amides, 3° amines, halogens, pseudohalogens, sterically demanding ortho-groups and even oxidatively sensitive aldehydes and primary alcohols. The tolerance of halogens is of particular note, as this provides an excellent handle for further functionalization by traditional cross-coupling methods. A summary of the scope is shown in Scheme 1 while a full list of examples is included in Table 1 at the end of the discussion section.

Limitations

As a result of the S_EAr mechanism, a nucleophilic arene is required to intercept the proposed electrophilic Au^{III} intermediate.[4] Thus, electron-deficient (hetero)arenes such as pyridine and fluorobenzene fail to undergo efficient coupling. Conversely, highly electron-rich (hetero)arenes can undergo oxidative decomposition or form diaryl-iodonium side-products by direct reaction with the I^{III} oxidant. While it may at first sound quite limiting

to use only moderately electron-rich arenes, the reality is that due to the nature of the aromatic motif, a vast array of synthetically useful arene substrates inherently lie within this reactivity window. For the aryl silane, highly electron-rich substrates can intercept the electrophilic Au^{III} intermediate and as a result, undergo competitive homocoupling. When economically viable, this can be overcome by employing an excess of the arene coupling partner.

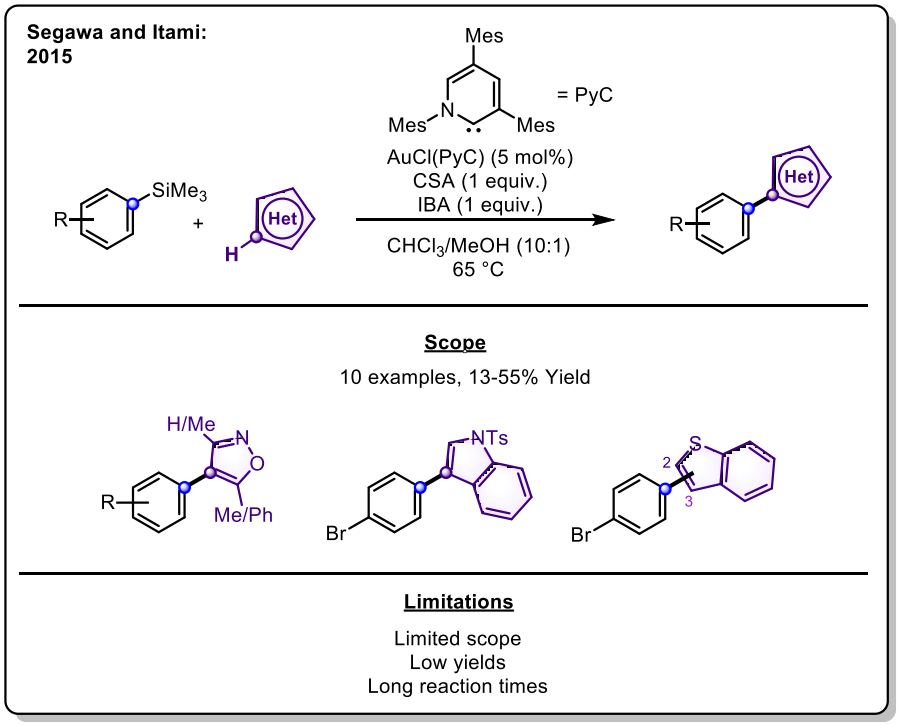


Scheme 1. Representative scope of the gold-catalyzed oxidative coupling of arenes and arylsilanes[3]

*Inter*molecular Coupling of Heteroarenes and Aryl Silanes – Segawa and Itami

Overview

In 2015 the groups of Segawa and Itami extended the methodology to include previously un-tolerated heteroarenes (Scheme 2).[5] This was accomplished through the use of a strongly electron-donating NHC ligand which the authors propose accelerates the rate of arylation and facilitates the Au^{I}-Au^{III} oxidation process.



Scheme 2. Representative scope of the gold-catalyzed oxidative coupling of heteroarenes and arylsilanes reported by Segawa and Itami[5]

Scope and Limitations

Although serving as a proof of concept the yields obtained were generally poor to moderate (13–55%), and the reaction quite slow (5 mol% catalyst, 65 °C, 18–48 h). As a result, the reported scope is quite small,

consisting of four isoxazoles, one indole and one benzothiophene. The aryl silanes investigated possessed limited functionality, comprising of halogens and one CF_3 group. A summary of the scope is shown in Scheme 2 while a full list of examples is included in Table 2 at the end of the discussion section.

*Inter*molecular Coupling of Heteroarenes and Aryl Silanes – Lloyd-Jones

Overview

In 2016 the Lloyd-Jones group published an alternative coupling of previously un-tolerated heteroarenes (Scheme 3).[6] This was accomplished through the use of $thtAuBr_3$ as a rapidly activating pre-catalyst, the exclusion of methanol as co-solvent and the use of tailored oxidants and aryl silane coupling partners. Specifically, the use of 2,4,6-triisopropyl-iodobenzene diacetate as a sterically hindered I^{III} oxidant helps prevent oxidative decomposition of the heteroarene and the formation of diaryliodonium salt side-products. Replacing the standard trimethylsilyl (TMS) group with a 3-hydroxypropyldimethylsilyl (HPDMS) group greatly accelerated the arylation, enabling facile coupling at room temperature, providing moderate to high yields (43 – 89%) generally within 3 h.

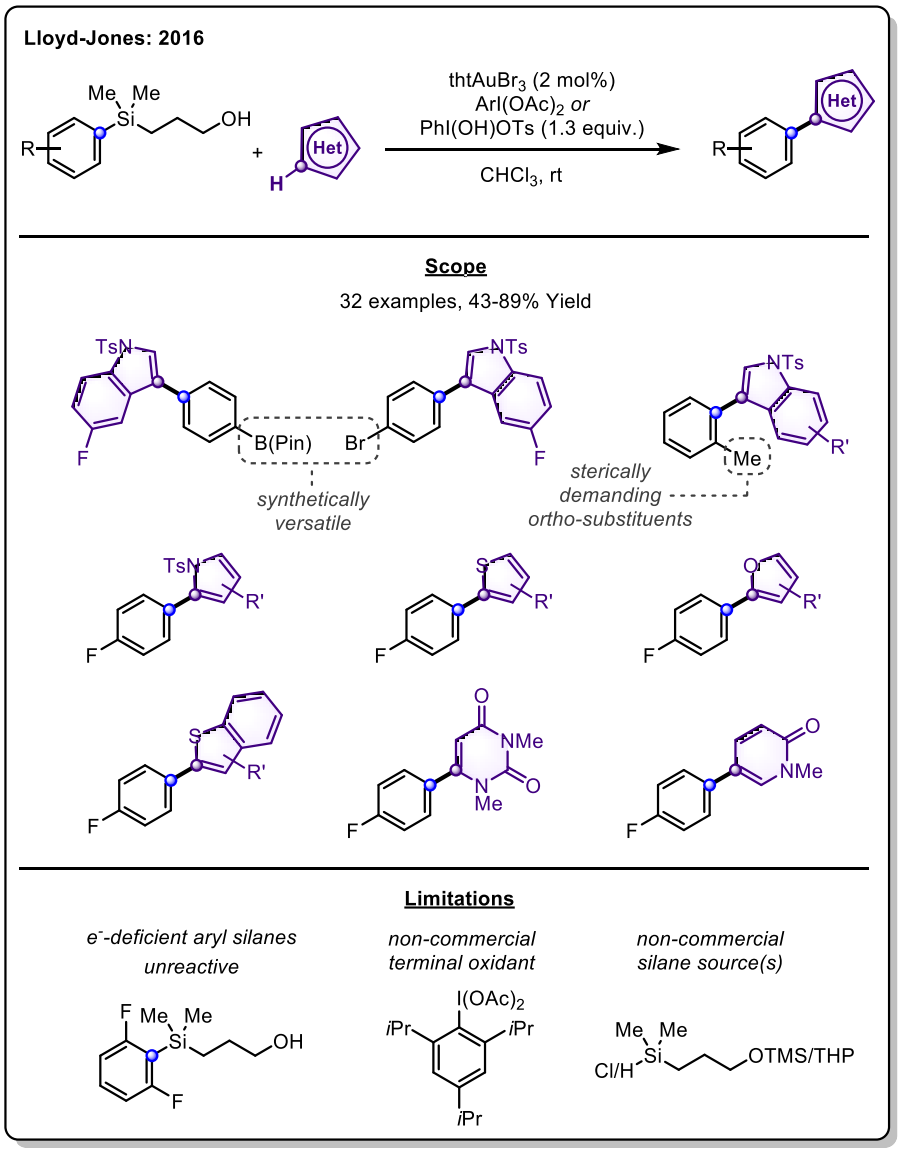
Scope

A range of heteroarenes were successfully coupled including indole, pyrrole, furan, thiophene, benzothiophene, uracil and 2-pyridone. Essentially quantitative (>95%) regioselectivity is obtained in all but one case. The reaction partners (Ar^1-H and Ar^2-$SiMe_3$) may possess a range of functionality including esters, halogens, silanes and boronic esters. The tolerance of boronic esters, halogens and silanes (TMS) provides an excellent handle for further functionalization by traditional cross-coupling methods. A summary of the scope is shown in Scheme 3 while a full list of examples is included in Table 3 at the end of the discussion section.

Limitations

Unsurprisingly, due to the diverse electronic nature of heteroarenes a total of 15 substrates examined failed to undergo productive hetero-coupling (Table 3). With respect to the aryl silane, electron-deficient substrates are unreactive under the current conditions. As an inconvenience rather than a limitation, the tailored reagents employed (sterically hindered terminal oxidant and silane source) are not commercially available and must be

prepared via relatively simple, chromatography-free syntheses.



Scheme 3. Representative scope of the gold-catalyzed oxidative coupling of heteroarenes and arylsilanes reported by Lloyd-Jones[6]

*Intra*molecular Coupling of Arenes and Aryl Silanes

Overview

In 2017 the Lloyd-Jones group published a preparative and mechanistic study on the *intra*molecular arylation of aryl silanes (Scheme 4).[7] This reaction was demonstrated to generate a range of 5- to 9-membered carbo- and hetero-cyclic rings under mild conditions, at room temperature. The majority of examples utilized 1-2 mol% Au and reached full conversion within a reasonable time scale. For some substrates, complete coupling was achieved in under 30 min, allowing the catalyst loading to be dropped as low as 0.06 mol%. As an additional benefit, the intramolecular nature of the reaction essentially eliminates competitive aryl silane homocoupling and facilitates the arylation of neutral and electron-deficient arenes, substrates that do not react at all in the intermolecular processes. As a demonstration, this methodology was applied in a formal synthesis of the natural product (±)-Allocolchicine.[8] For highly electron-rich substrates, the formation of diaryliodonium salts by direct reaction with the $ArIX_2$ oxidant is an unwanted side-reaction for both intra- and intermolecular coupling. For some intramolecular arylations the use of a milder oxidant, phenyliodine bis(trifluoroacetate) (PIFA) can diminish this side-reaction while still facilitating productive catalysis. It should be noted that PIFA does not facilitate productive catalysis for the intermolecular coupling.

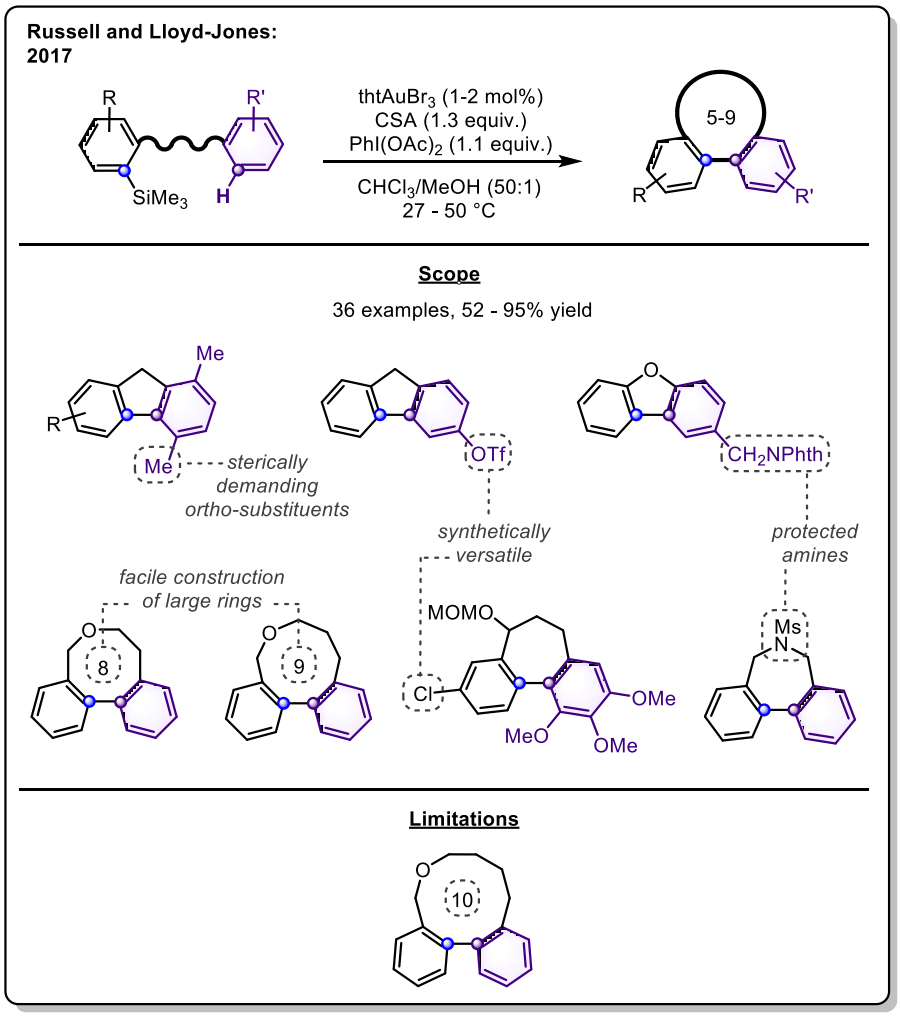
Scope

The aryl silane can be functionalized with halogens, sterically demanding ortho-groups and may be electron-rich, neutral or electron-deficient. The arene can be functionalized with ethers, halogens, pseudohalogens, sterically demanding ortho-groups and may also be electron-rich, neutral or electron-deficient, a feature unique to the intramolecular process. The tether may contain heteroatoms (N and O investigated) with 10 examples reported ranging from 5- to 9-membered carbo- and hetero-cyclic rings. A summary of the scope is shown in Scheme 4 while a full list of examples is included in Table 4 at the end of the discussion section.

Limitations

One substrate which could potentially form a 10-membered ring failed to undergo productive coupling. However, the formation of larger rings (10+) has not been exhaustively investigated and this may still be possible

depending on the substrate. The intramolecular coupling of heteroarenes has not been reported, either with arylsilanes or heteroarylsilanes and is currently under investigation in this research group.



Scheme 4. Representative scope of the gold-catalyzed intramolecular cylization of arenes and arylsilanes[7,8]

General Procedure

Herein we report a detailed procedure for the preparation and cyclization of 1-trimethylsilyl-2-(phenoxymethyl)benzene as a general example for the arylation of aryl silanes. The gold-catalyzed coupling itself is operationally simple and has proven to be a highly robust reaction over the past 6 years of study within our group. A high-yielding preparation of the requisite pre-catalyst, tetrahydrothiophene gold tribromide ($thtAuBr_3$) is also reported. This pre-catalyst shows minimal induction period (<300 s) and is stable both in the solid-state and in solution.

Additional Considerations:

Prediction of regioselectivity using RegioSQM

Jørgensen and co-workers recently (2018) reported a computational method to predict the preferred site of electrophilic aromatic substitution for arenes and heteroarenes.[9] The prediction is easy to carry out for non-experts, requiring the user to simply copy a SMILES string of the substrate (generated in ChemDraw) to an online tool (http://www.regiosqm.org) made freely available to the public. The structure is returned in a matter of minutes with the reactive site(s) highlighted. Retrospective analysis of a random selection of gold-catalyzed intermolecular couplings of (hetero)arenes and aryl silanes show that regioselectivity can be predicted with a success rate of 87% for the major regioisomer (40 out of 46 examples). This method also highlights alternative reactive sites on the (hetero)arene, which can help to predict problematic regiochemistry issues a priori.

Solvent

Chloroform, either with or without methanol as a co-solvent, is employed as the primary solvent in all reported couplings thus far. While suitable for small scale investigations, its high toxicity and environmental impact would necessitate a replacement for any large scale application. Examination of alternative solvents within our group has previously led to mixed results, however, in most cases ethyl acetate acts as a suitable replacement, albeit with much slower reaction rates. Investigations into a general, alternative solvent are currently on-going in our research group.

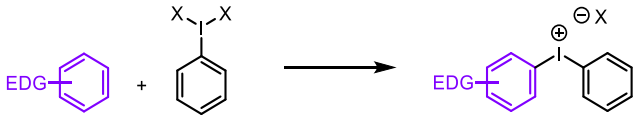
Oxidant

For relatively small scale applications (<100 g) the use of $PhIX_2$ reagents

such as $PhI(OAc)_2$ and PIFA as terminal oxidants in not an issue. However, the use of such reagents on a large scale is not ideal due to their high cost and the high mass of stoichiometric by-products. Investigations into a general, alternative terminal oxidant are currently on-going in our research group.

Formation of diaryliodonium side-products

With highly electron-rich arenes it is common for a competitive reaction between the arene and the electrophilic I^{III} oxidant to take place, furnishing a diaryliodonium salt side-product (Scheme 5). We have shown that in the intramolecular coupling, this can be mitigated by the use of PIFA as a less electrophilic I^{III} oxidant.



Scheme 5. Formation of diaryliodonium salt side-product

Formation of proto- and bromodesilylated side-products

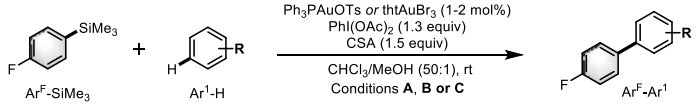
Highly electron rich arylsilanes are often subject to competing S_EAr reactions with opportunistic electrophiles present in the reaction mixture. Under our standard conditions both H^+ and Br^+ are present (from CSA and $thtAuBr_3$ respectively) resulting in small amounts of proto- and bromodesilylation in some cases (Scheme 6). The amount of bromodesilylation observed is dependent on the quantity of precatalyst employed, with $thtAuBr_3$ releasing 2 equivalents of Br^+, at typical catalyst concentrations this results in up to 2-4% bromodesilylation.

Scheme 6. Formation of proto- or bromodesilylated side-products

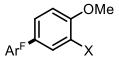
Removal of the iodobenzene side-product

Stoichiometric quantities of iodobenzene are generated when using $PhI(OAc)_2$ or PIFA as a terminal oxidant. For sufficiently polar products, this can be removed by a simple silica-gel plug, eluting with petroleum ether. For non-polar products, this must be removed by (usually facile) column chromatography.

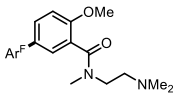
Table 1. Scope of the gold-catalyzed coupling of arenes and arylsilanes[3,4]



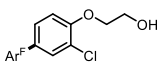
Conditions A: Ar^1-H (1.0 equiv), $Ph_3PAuOTs$ (2 mol%)



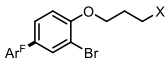
1	X = Cl	85%
2	X = Br	92%
3	X = I	88%
4	X = OMs	81% [a]
5	X = CO_2Me	92%
6	X = NMePiv	94%
7	X = NPhth	88%



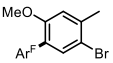
8 65% [b]



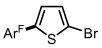
9 59% [c]



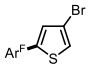
10	X = OH	82% [d]
11	X = OMs	71%
12	X = $OCONEt_2$	69%
13	X = NPhth	83%



14 74%



15 91%

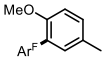


16 29% [e]

[a] 1.5 equiv of Ar^1-H. [b] IBA instead of $PhI(OAc)_2$ at 65 °C. [c] 1.5 mol% Au. [d] With X = $OSiiPr_3$, in situ deprotection yields **10** (63%). [e] Site selectivity: 57%, with 2,5-diarylated thiophene (17%) also formed.

Conditions B: Ar^1-H (2.0 equiv), $Ph_3PAuOTs$ (1 mol%).

17 68% [f]



18 63% [g]

19 46% [h]

20 93% [i]

21 82% [j]

22 71%

23 74%

24 74%

25 65%

26 78% [a]

27 57% [k]

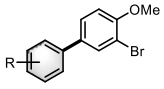
28 37% [l]

29 6% [m]

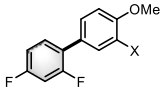
30 0%

[f] Site selectivity: 89%. [g] 2,6-Diarylated anisole (10%). [h] Site selectivity: 67%, diarylated anisole (8%). [i] Site selectivity: 80%. [j] Site selectivity: 87%. [k] 1.0 equiv of Ar^1-H. [l] 4,4′-Difluorobiphenyl (homocoupling product, 37%) and 1,4-diarylated benzene (10%) also formed. [m] ArBr = 4-bromophenyl.

Conditions A: Ar^1-H (1.0 equiv), $Ph_3PAuOTs$ (2 mol%)



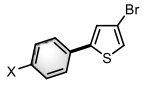
31	R = 2-F	92% [b]
32	R = 2-OMs	70% [b]
33	R = 4-Cl	97%
34	R = 4-Br	91%
35	R = 4-I	67%
36	R = 3-Br	72%
37	R = 3-CHO	77%
38	R = 4-Piv	90%
39	R = 4-CO_2Me	70%
40	R = 4-OTf	72% [n]
41	R = 4-OPiv	80%
42	R = 4-NMePiv	59% [o]
43	R = 4-NMeTs	91%
44	R = H	84% [o]
45	R = 4-Me	55% [p]



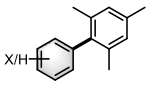
46	X = CO_2Me	70%
47	X = I	97%

[n] 1 mol% Au [o] Using Conditions B, arylsilane homocoupling (29%) also formed [p] IBA instead of $PhI(OAc)_2$ at 65 °C, Ar^1-H (2 equiv), arylsilane homocoupling (23%) also formed

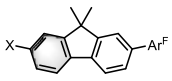
Conditions C: Ar^1-H (2.0 equiv), $thtAuBr_3$ (1.4 mol%)
(Not isolated, prepared as part of kinetic studies)[4]



48	X = Me
49	X = CO_2Me
50	X = F
51	X = Br

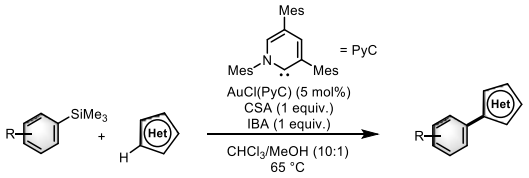


52	X = *p*-Me
53	X = *p*-F
54	X = *p*-Br
55	X = *p*-CF_3
56	X = *p*-I
57	X = *p*-Cl
58	X = *p*-CO_2Me
59	X = *m*-Br
60	X = *m*-Me



61	X = H
62	X = Me
63	X = Bn
64	X = CH_2OMe
65	X = C_6H_4Cl
66	X = Br
67	X = OMs
68	X = CO_2Me

Table 2. Scope of the gold-catalyzed coupling of heteroarenes and arylsilanes[5]



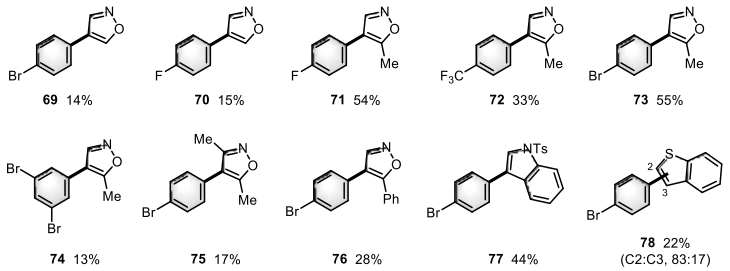


Table 3. Gold-catalyzed coupling of heteroarenes and arylsilanes[6]

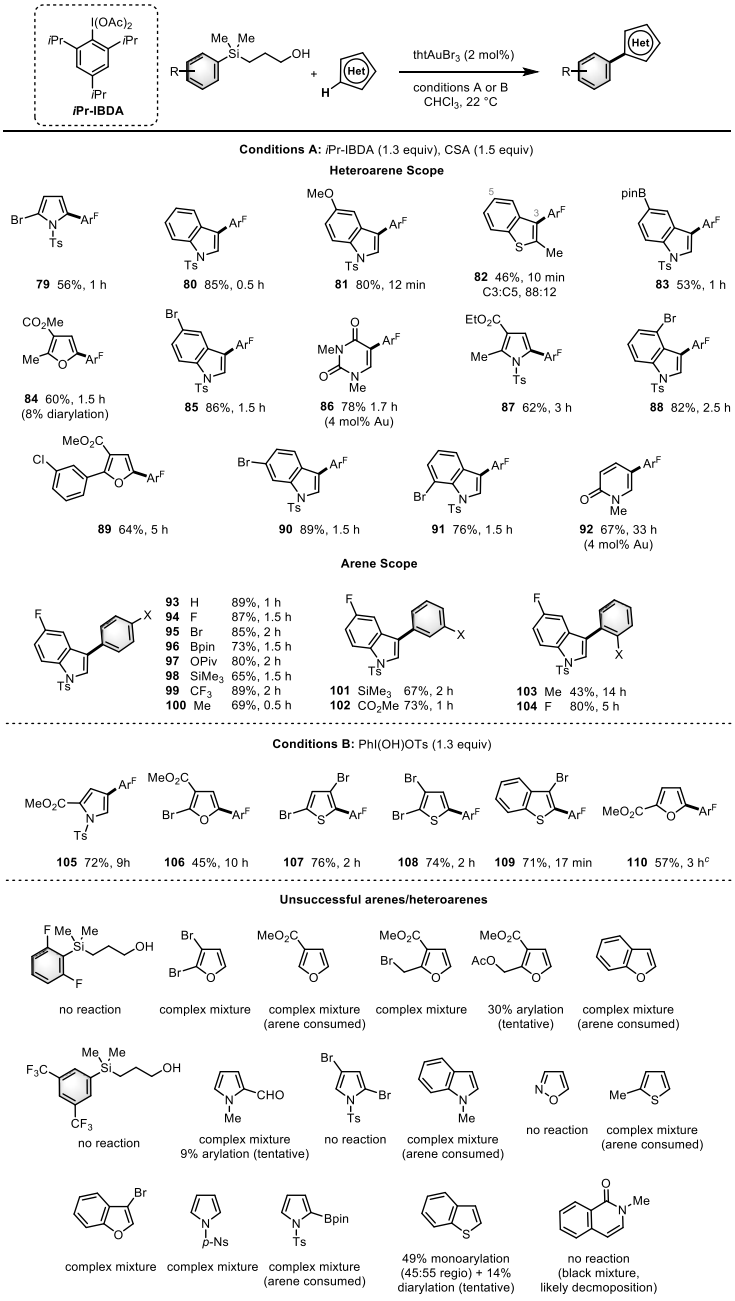
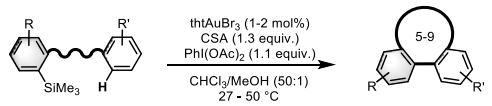
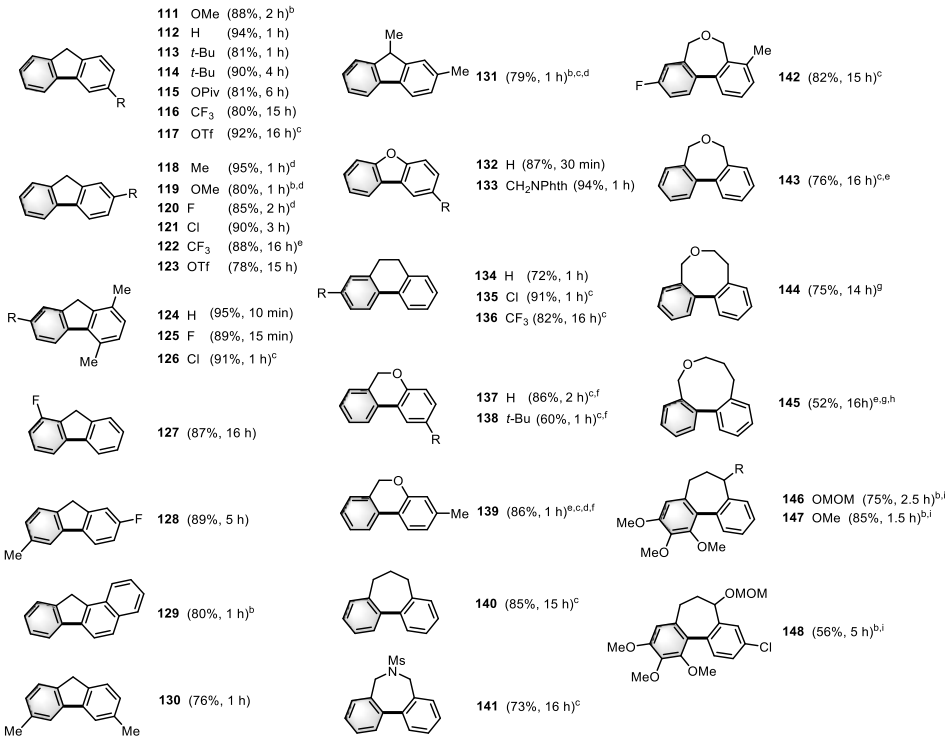


Table 4. Scope of the intramolecular gold-catalyzed coupling of arenes and arylsilanes[7,8]





[a]Unless otherwise stated: ArH (0.50 mmol), thtAuBr$_3$ (1 mol%), PhI(OAc)$_2$ (0.55 mmol), CSA (0.65 mmol) in CHCl$_3$/MeOH (50:1, 0.1 M). [b]PhI(OCOCF$_3$)$_2$, (0.55 mmol) replaces PhI(OAc)$_2$/CSA. [c]thtAuBr$_3$ (2 mol%). [d]Ratio of 2-/4-regioisomers: **118** (95:5), **119** (88:12), **120** (97:3), **131** (97:3) and 3-/1-regioisomers: **139** (89:11). [e]CSA (1.0 mmol). [f]0.05 M substrate. [g]thtAuBr$_3$ (4 mol%). [h]50 °C. Phth = phthalimido. Piv= t-BuCO$_2$ [i]thtAuBr$_3$ (5 mol%)

References

1. Current address: University of Edinburgh, EaStChem, Joseph Black Building, David Brewster Road, Edinburgh, EH9 3FJ, U.K. Email: guy.lloyd-jones@ed.ac.uk. The research leading to these results has

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8. Corrie, T. J. A.; Lloyd-Jones, G. C. *Topics in Catalysis*, **2017**, *60*, 570–579.
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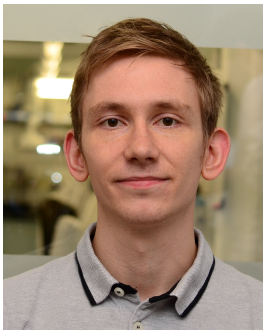
Appendix
Chemical Abstracts Nomenclature (Registry Number)

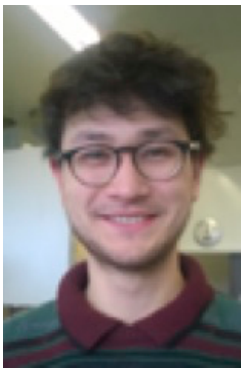
Gold (III) bromide: Gold bromide; (10294-28-7)
Tetrahydrothiophene: Thiophene, tetrahydro-; (110-01-0)
Potassium carbonate: Carbonic acid, dipotassium salt; (584-08-7)
Phenol: Phenol; (108-95-2)
2-Bromobenzyl bromide: Benzene, 1-bromo-2-(bromomethyl)-: (3433-80-5)
n-Butyllithium: Lithium, butyl-; (109-72-8)
Chlorotrimethylsilane: Silane, chlorotrimethyl-; (75-77-4)
Magnesium sulfate: Sulfuric acid magnesium salt (1:1); (7487-88-9)
Diphenylacetic acid: Benzeneacetic acid, α -phenyl-; (117-34-0)
Sodium sulfate: Sulfuric acid disodium salt; (7757-82-6)
(±)-Camphor-10-sulfonic acid: Bicyclo[2.2.1]heptane-1-methanesulfonic acid, 7,7-dimethyl-2-oxo; (5872-08-2)
(Diacetoxyiodo)benzene: Iodine, bis(acetato-κO)phenyl-; (3240-34-4)
Sodium carbonate: Carbonic acid disodium salt; (497-19-8)

Guy Lloyd-Jones FRS studied Chemical Technology at Huddersfield, obtained his doctorate at Oxford with John Brown FRS, and did postdoctoral research with Andreas Pfaltz at Basel. He began his independent career in 1996 at the University of Bristol, building a research group specializing in kinetics, NMR and isotopic labelling. In 2013 he moved to take up The Forbes Chair at the University of Edinburgh and in the same year was elected to the UK National Academy of Science (FRS).



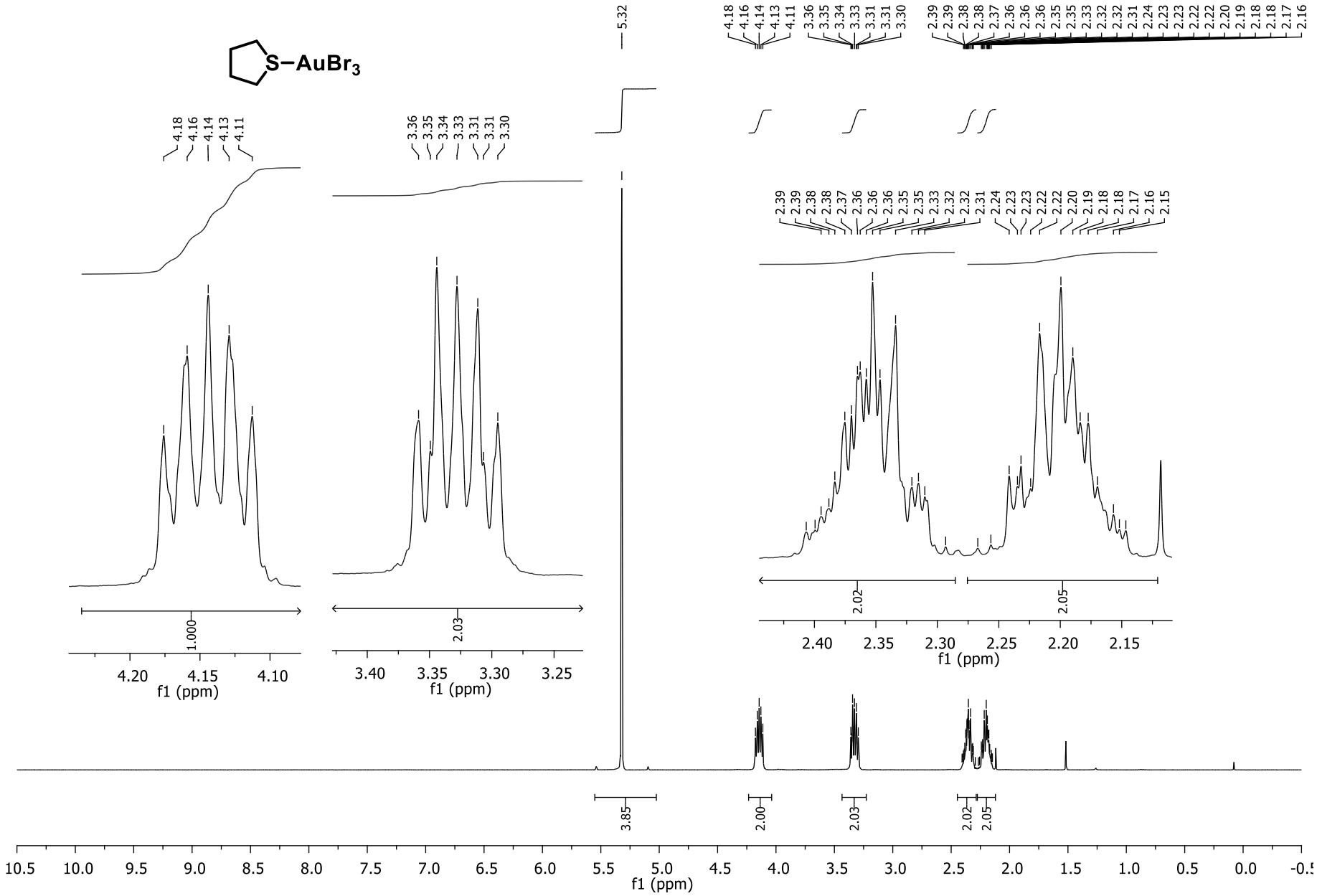
Chris Nottingham completed a B.Sc. in Chemical and Pharmaceutical Science at the Galway-Mayo Institute of Technology in 2012 before obtaining a Ph.D. in organic chemistry under the supervision of Prof. Patrick Guiry MRIA at University College Dublin in 2016. After postdoctoral research at the University of Edinburgh under the direction of Prof. Guy C. Lloyd-Jones FRS, he joined GlaxoSmithKline in Ireland.

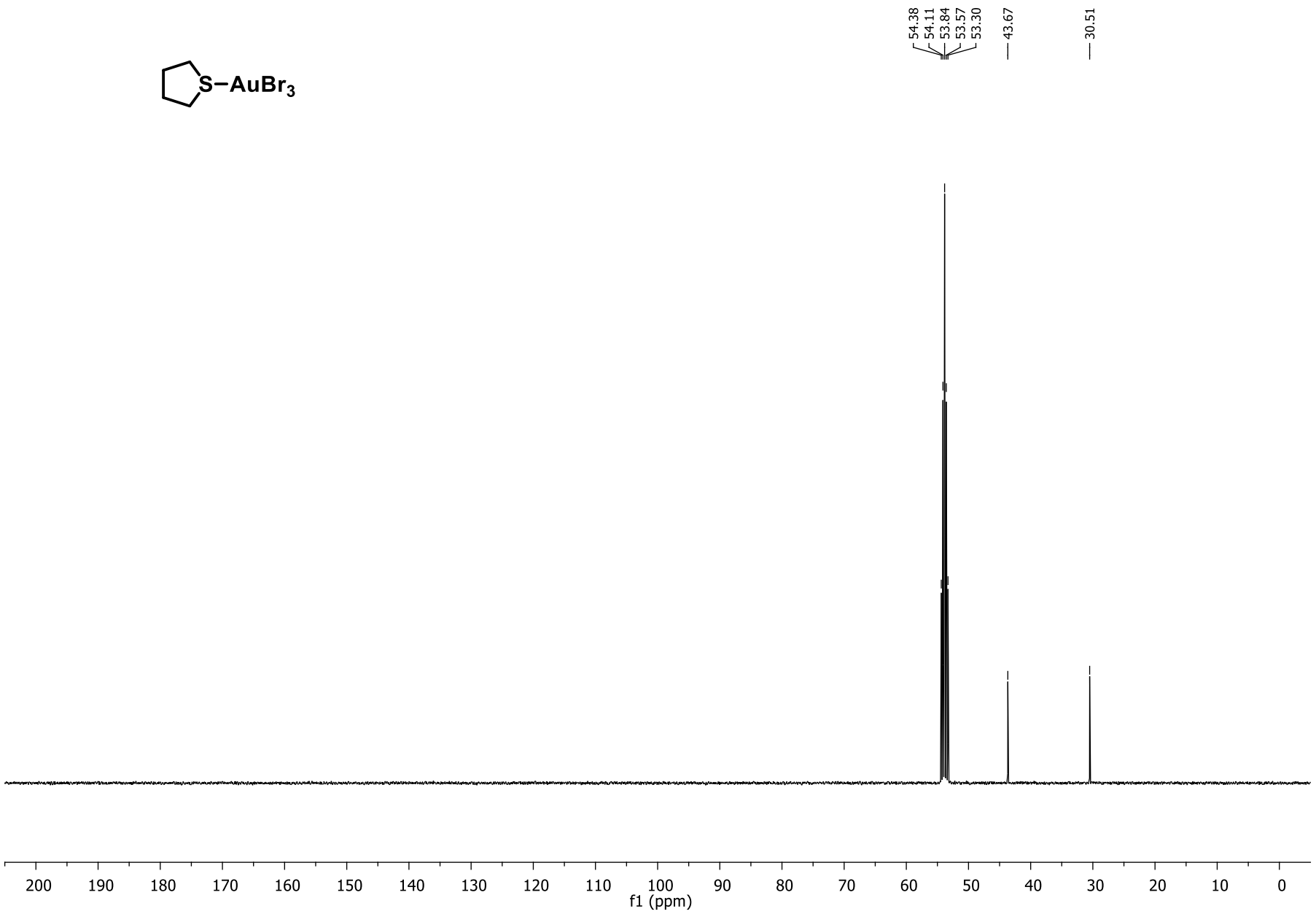
Verity Barber obtained a master's degree in Medicinal and Biological Chemistry at the University of Edinburgh. She completed her masters project work in the group of Prof. Guy Lloyd-Jones FRS. As part of her degree, she also spent a year in the laboratory of Catalysis and Organic Synthesis at EPFL, under the supervision of Prof. Jérôme Waser.



Alexandre Genoux obtained his master's Degree in Chemistry from the Joseph Fourier University (Grenoble-France) in 2015. During his studies, he joined the group of Prof. Liming Zhang at the University of California, Santa Barbara (USA) to work as a visiting student (2014), followed by a stay at the University of Cambridge (UK) in the group of Dr. Robert Phipps for his master thesis (2015). In January 2016 he started his Ph.D. at the University of Zurich in the group of Prof. Cristina Nevado where he is working on the reactivity of new gold(III) complexes and their application in the development of new cross-coupling reactions.

Estíbaliz Merino obtained her Ph.D. degree from the Autónoma University (Madrid-Spain). After a postdoctoral stay with Prof. Magnus Rueping at Goethe University Frankfurt and RWTH-Aachen University in Germany, she worked with Prof. Avelino Corma in Instituto de Tecnología Química-CSIC (Valencia) and Prof. Félix Sánchez in Instituto de Química Orgánica General-CSIC (Madrid) in Spain. At present, she is a research associate in Prof. Cristina Nevado´s group at the University of Zürich. She is interested in the synthesis of natural products using catalytic tools and in the development of new materials with application in heterogeneous catalysis.


S–AuBr3
5.32
4.18 4.16 4.14 4.13 4.11
3.36 3.35 3.34 3.33 3.31 3.31 3.30
2.39 2.39 2.38 2.38 2.37 2.36 2.36 2.36 2.35 2.35 2.33 2.32 2.32 2.31 2.24 2.23 2.23 2.22 2.22 2.20 2.19 2.18 2.18 2.17 2.16 2.15
1.000
2.03
2.02
2.05
4.20 4.15 4.10
3.40 3.35 3.30 3.25
2.40 2.35 2.30 2.25 2.20 2.15
f1 (ppm)
3.85
2.00
2.03
2.02
2.05
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


S–AuBr3
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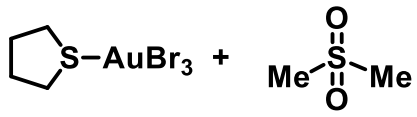
54.11
53.84
53.57
53.30
43.67
30.51
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



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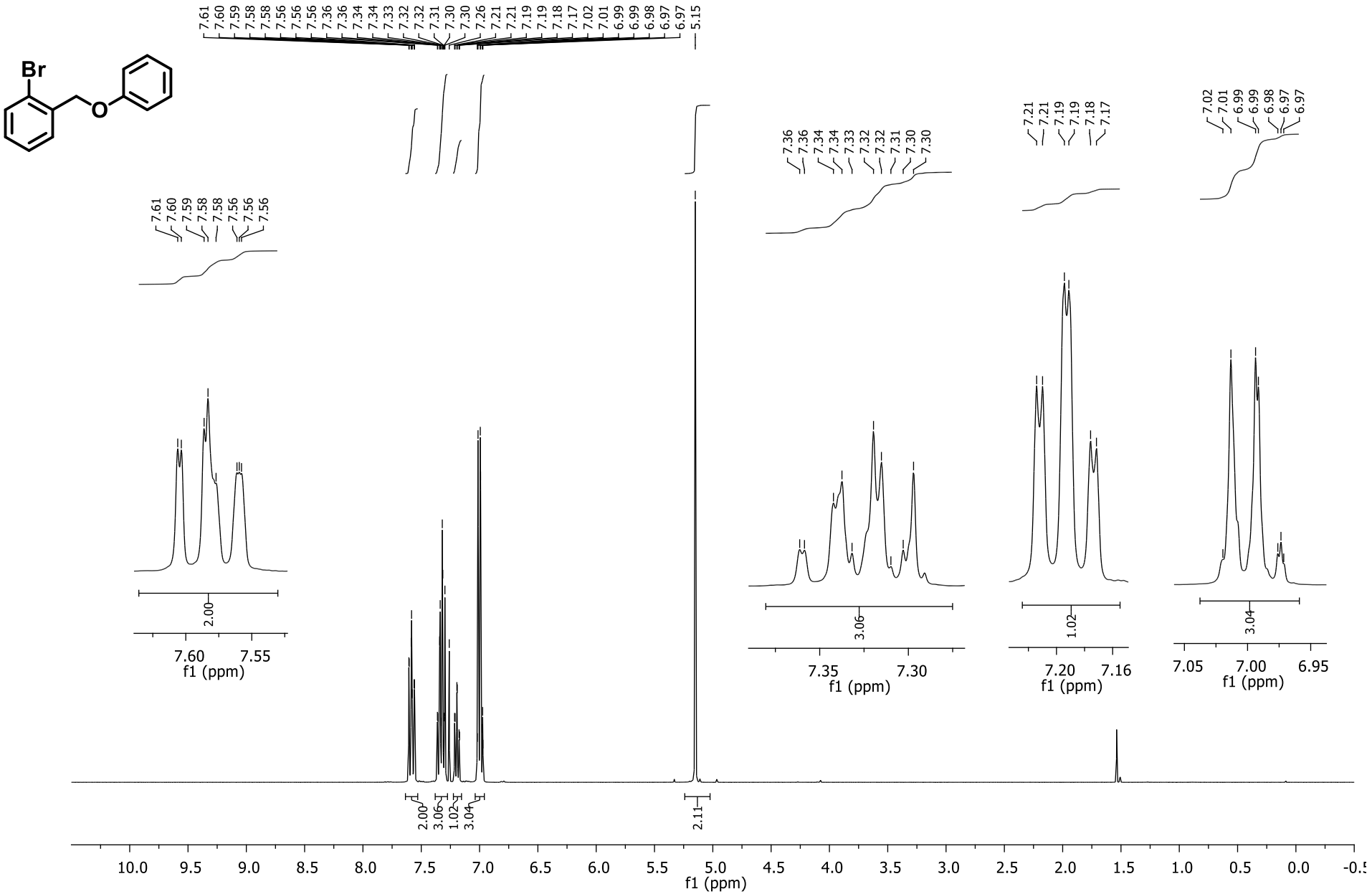
Standard Purity	0,9996	
Purity (%)	98,57%	

Full scale


Br
O
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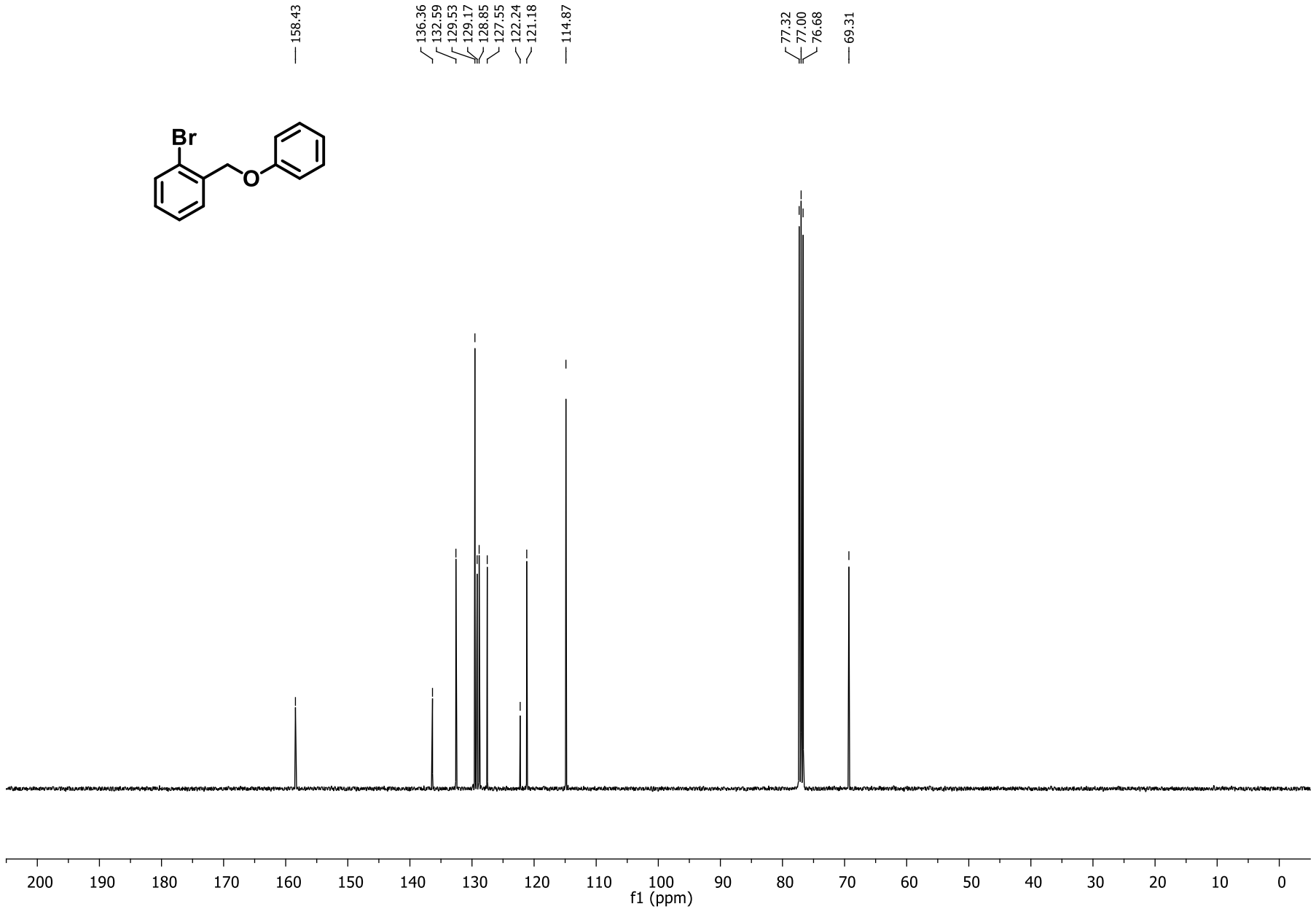
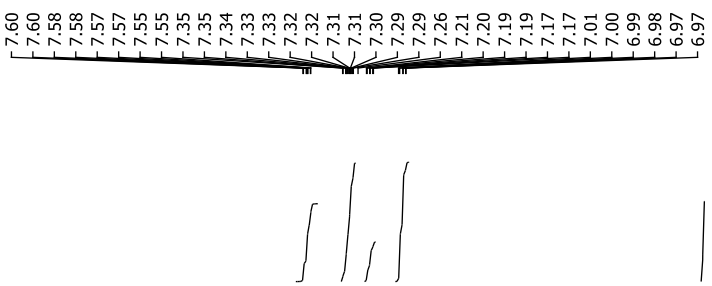
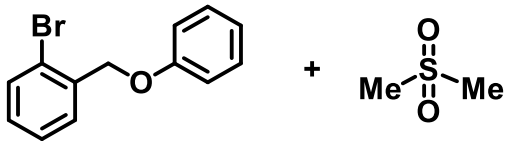
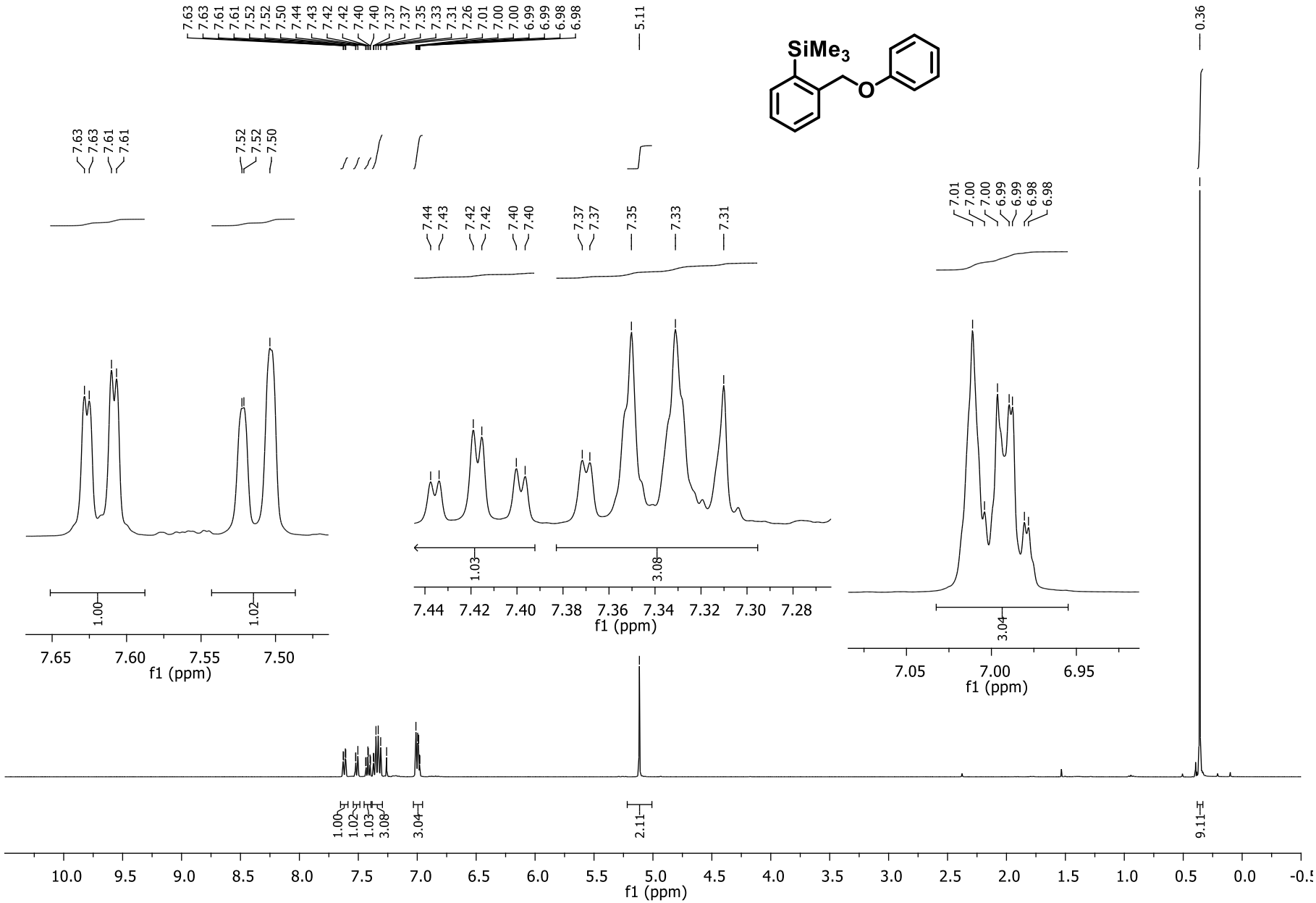
7.61 7.60 7.59 7.58 7.58 7.56 7.56 7.56
2.00
7.60 7.55
f1 (ppm)
7.36 7.36 7.34 7.34 7.33 7.32 7.32 7.31 7.30 7.30
3.06
7.35 7.30
f1 (ppm)
7.21 7.21 7.19 7.19 7.18 7.17
1.02
7.20 7.16
f1 (ppm)
7.02 7.01 6.99 6.99 6.98 6.97 6.97
3.04
7.05 7.00 6.95
f1 (ppm)
2.00 3.06 1.02 3.04 2.11
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

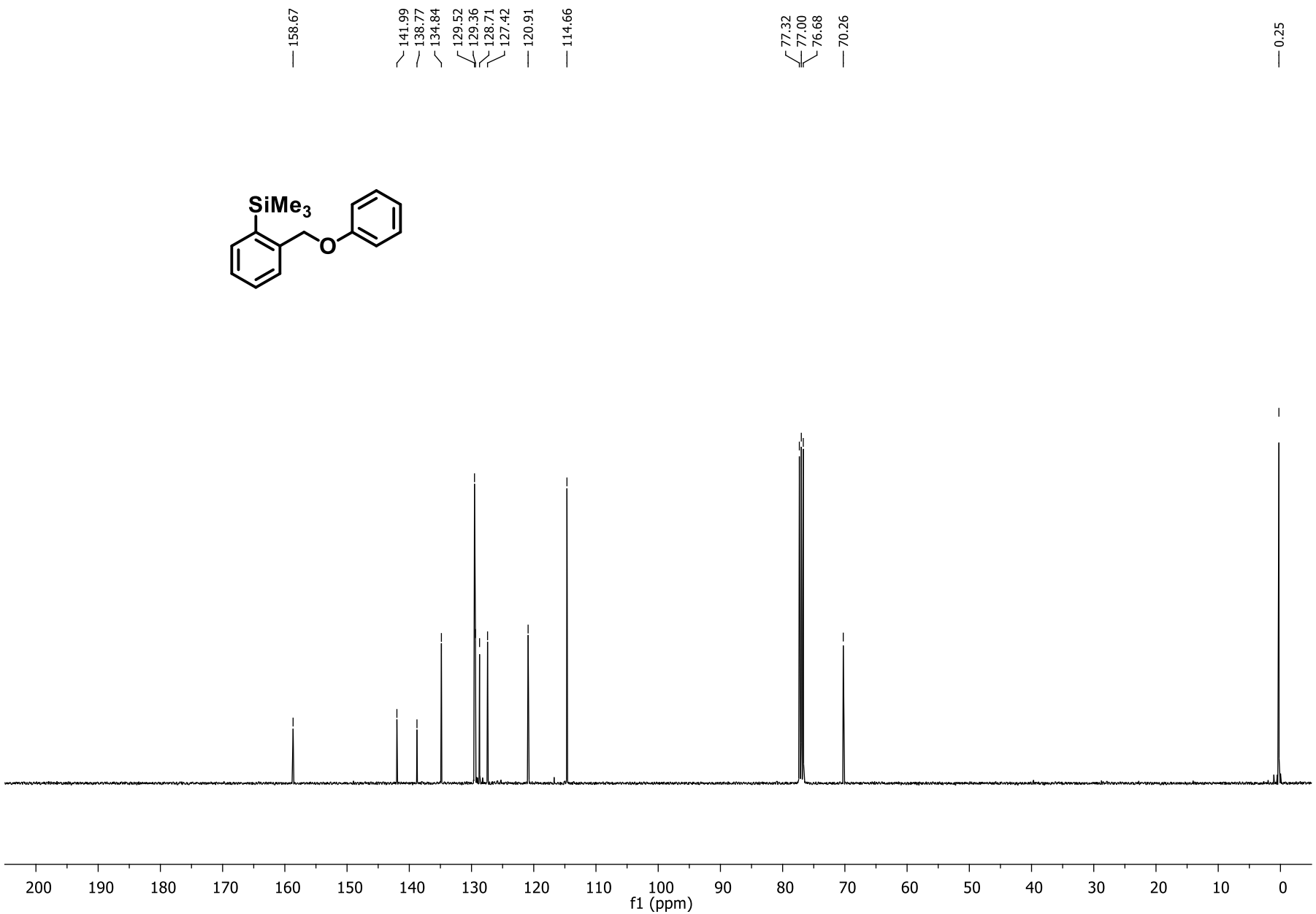

158.43
136.36
132.59
129.53
129.17
128.85
127.55
122.24
121.18
114.87
77.32
77.00
76.68
69.31
Br
O
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



	MW	mg
IS	94,13	6,83
Compound	263,13	19,54
Standard Purity	0,9996	
Purity (%)	98,69%	




7.63 7.63 7.61 7.61 7.52 7.52 7.50 7.44 7.43 7.42 7.42 7.40 7.40 7.37 7.37 7.35 7.33 7.31 7.26 7.01 7.00 7.00 6.99 6.98 6.98
5.11
0.36
SiMe3
O
1.00
1.02
1.03
3.08
3.04
2.11
9.11
f1 (ppm)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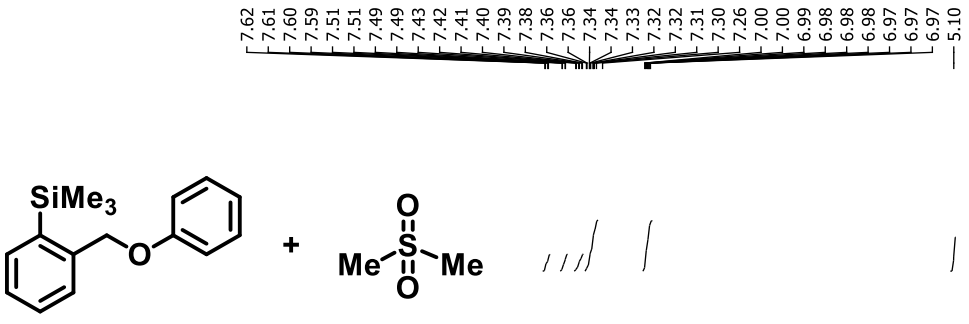
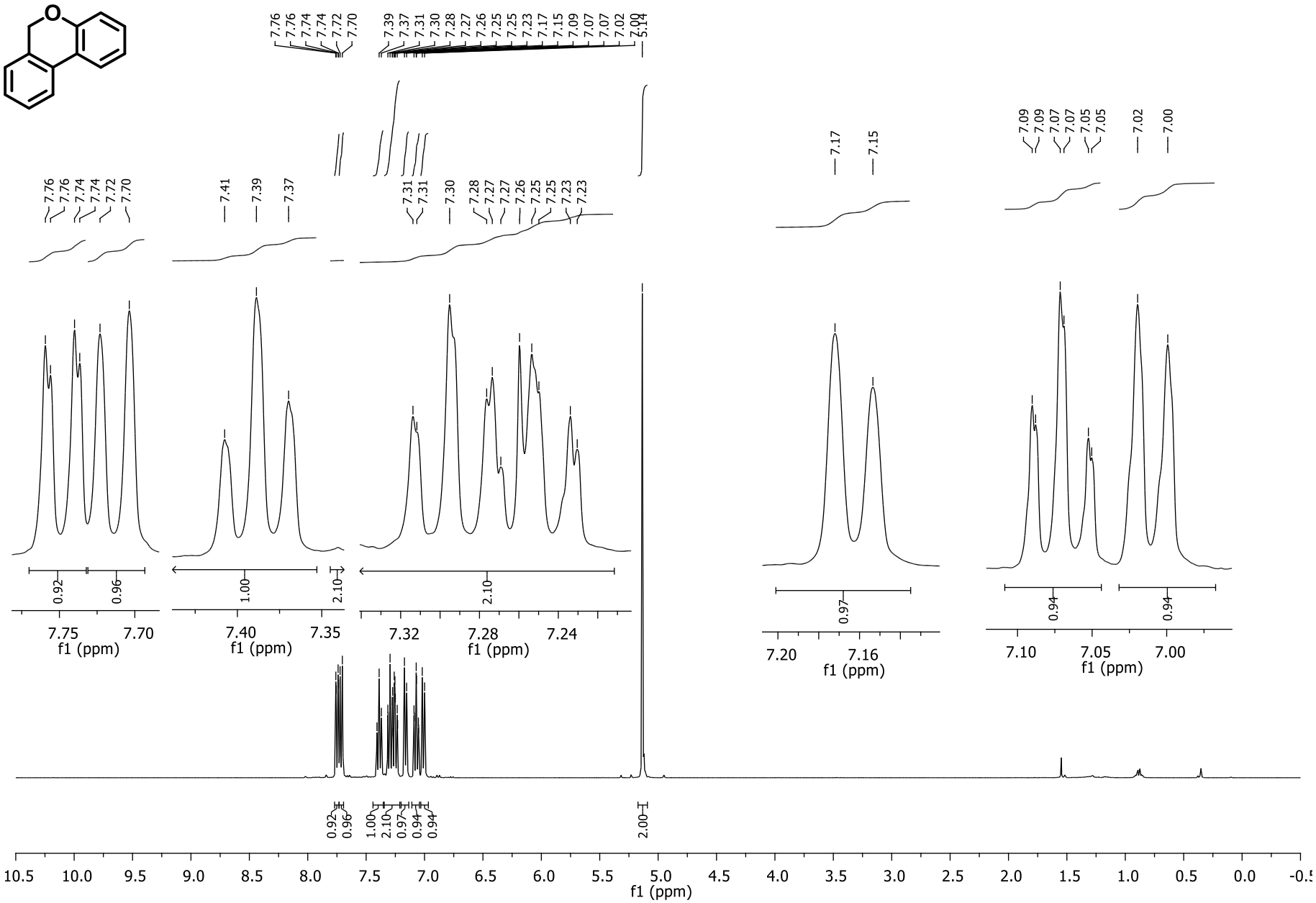
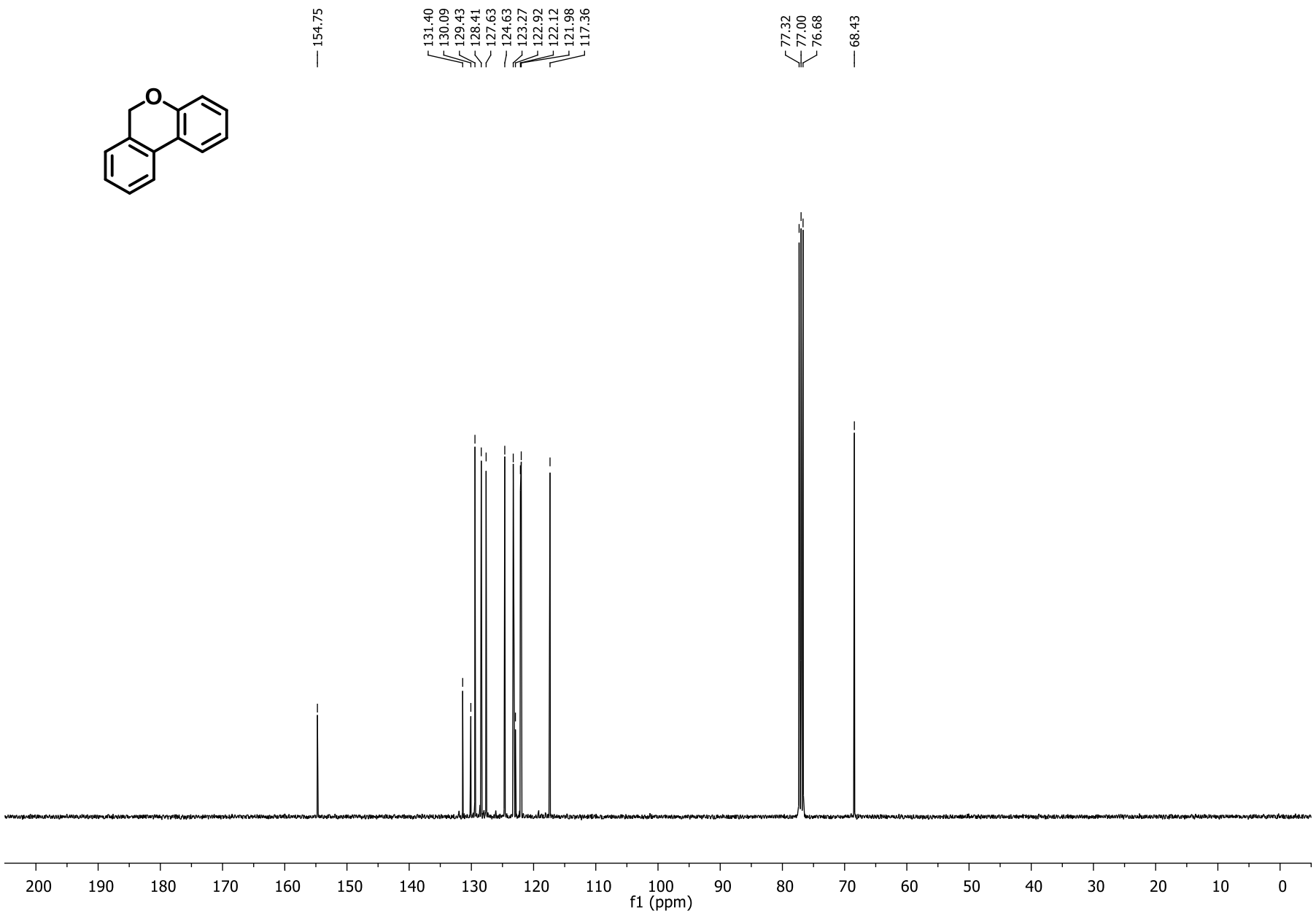
141.99
138.77
134.84
129.52
129.36
128.71
127.42
120.91
114.66
77.32
77.00
76.68
70.26
0.25
SiMe3
O
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

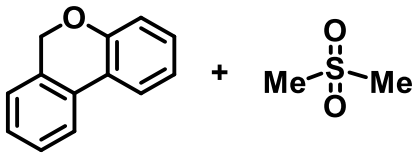


Full scale

	MW	mg
IS	94,13	7,25
Compound	256,42	19,95
Standard Pur	0,9996	
Purity (%)	97,83%	


7.76 7.76 7.74 7.74 7.72 7.70
7.39 7.37 7.31 7.30 7.28 7.27 7.26 7.25 7.25 7.23 7.17 7.15 7.09 7.07 7.07 7.02 7.00 5.14
7.41 7.39 7.37
7.31 7.31 7.30 7.28 7.27 7.27 7.26 7.25 7.25 7.23 7.23
7.17 7.15
7.09 7.09 7.07 7.07 7.05 7.05 7.02 7.00
0.92 0.96 1.00 2.10 2.10 0.97 0.94 0.94 2.00
f1 (ppm)


154.75
131.40
130.09
129.43
128.41
127.63
124.63
123.27
122.92
122.12
121.98
117.36
77.32
77.00
76.68
68.43
O
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



Full scale

	MW	mg
IS	94,13	8,93
Compound	182,22	17,55
Standard Pur	0,9996	
Purity (%)	96,96%